Review Article

Checkpoint Inhibitors

The Diagnosis and Treatment of Side Effects

Lucie Heinzerling, Enrico N. de Toni, Georg Schett, Gheorghe Hundorfean, and Lisa Zimmer

Summary

Background: Treatment with checkpoint inhibitors such as anti-programmed death-1 (anti-PD-1), anti-PD-ligand 1 (anti-PD-L1), and anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4) antibodies can prolong the survival of cancer patients, but it also induces autoimmune side effects in 86–96% of patients by activating the immune system. In 17–59% of patients, these are severe or even life-threatening.

Methods: This review is based on pertinent articles retrieved by a search in PubMed and on an evaluation of a side-effect registry.

Results: Checkpoint-inhibitor-induced autoimmune side effects manifest themselves in all organ systems, most commonly as skin lesions (46–62%), autoimmune colitis (22–48%), autoimmune hepatitis (7–33%), and endocrinopathies (thyroiditis, hypophysitis, adrenalitis, diabetes mellitus; 12–34%). Rarer side effects include pneumonitis (3–8%), nephritis (1–7%), cardiac side effects including cardiomyositis (5%), and neurological side effects (1–5%). Severe (sometimes lethal) side effects arise in 17–21%, 20–28%, and 59% of patients undergoing anti-PD-1 and anti-CTLA-4 antibody treatment and the approved combination therapy, respectively. With proper monitoring, however, these side effects can be recognized early and, usually, treated with success. Endocrine side effects generally require long-term hormone substitution. Patients who have stopped taking checkpoint inhibitors because of side effects do not show a poorer response of their melanoma or shorter survival in comparison to patients who continue to take checkpoint inhibitors.

Conclusion: The complex management of checkpoint-inhibitor-induced side effects should be coordinated in experienced centers. The creation of an interdisciplinary "tox team" with designated experts for organ-specific side effects has proven useful. Prospective registry studies based on structured documentation of side effects in routine clinical practice are currently lacking and urgently needed.

Cite this as:
Heinzerling L, de Toni E, Schett G, Hundorfean G, Zimmer L:
Checkpoint inhibitors—the diagnosis and treatment of side effects.
Dtsch Arztebl Int 2019; 116: 119–26. DOI: 10.3238/arztebl.2019.0119

Department of Dermatology, University Hospital Erlangen-Nürnberg: Prof. Dr. med. Lucie Heinzerling, MPH

Department of Internal Medicine II, University Hospital, Ludwig-Maximilians-University (LMU) Munich: PD Dr. med. Enrico de Toni

Department of Medicine 3, University Hospital Erlangen-Nürnberg: Prof. Dr. med. Georg Schett

Department of Medicine 1, University Hospital Erlangen-Nürnberg: Dr. med. Gheorghe Hundorfean

Clinic for Dermatology, Essen University Hospital, University of Duisburg-Essen: PD Dr. med. Lisa Zimmer

Immune checkpoint inhibitors activate anti-tumor defenses either through the disruption of inhibitory interactions between antigen-presenting cells and T lymphocytes at so-called checkpoints (anti-PD-1/PD-L1, anti-CTLA-4, anti-TIM-3, anti-LAG-3) or else through the stimulation of activating checkpoints (CD27, CD40, GITR, CD137). They are now used to treat various types of cancer, including lung cancer, renal cell carcinoma, Merkel cell carcinoma, Hodgkin's lymphoma, and urothelial carcinoma *(eTable)* and special groups of patients, e.g., patients with microsatellite instability (1). In patients with metastatic melanoma, the anti-CTLA-4 antibody ipilimumab, the anti-PD-1 antibodies nivolumab and pembrolizumab, and combination therapy with ipilimumab and an anti-PD-1 antibody can prolong survival and induce response rates of 19% (2), 36–44% (2, 3), and 58–61% (2, 4), respectively. Severe and even life-threatening side effects (classified according to the Common Terminology Criteria for Adverse Events" [CTCAE]; grade 3/4) arise in 17–21% of patients receiving anti-PD-1 monotherapy (2, 3), 20–28% of those receiving ipilimumab (2, 3), 45% of those receiving ipilimumab (1 mg/kg) plus pembrolizumab (4), and 59% of those receiving approved combination therapy with ipilimumab (3 mg/kg) and nivolumab (2) *(Table 1)*.

Immune checkpoint inhibitors often induce autoimmune side effects, which can affect all organ systems. These differ from the corresponding spontaneously occurring autoimmune diseases in many ways, including phenotypically, histologically, and serologically. The mechanisms of autoimmune side effects include the activation of T lymphocytes with infiltration of the organ in question (5), direct binding of the checkpoint inhibitor with activation of complement (CTLA-4 expression in the pituitary gland) (6), and immune reactions due to soluble factors (autoantibodies, cytokines). Moreover, the intestinal microbiome seems to influence the development of side effects (7, 8). No predictive factors for the appearance of side effects have yet been identified.

Common side effects include colitis, hepatitis, skin reactions, and endocrinopathies (thyroiditis or hypophysitis); rarer ones are myositis, cardiomyositis, and neurological side effects. The side effects are usually readily controllable. Checkpoint inhibitor treatment must be discontinued because of side effects in 7–12% of patients receiving anti-PD-1 therapy, 9–16% of those receiving ipilimumab therapy (2, 3), and 39% of those receiving combination therapy (2).

TABLE 1

Therapy-induced side affects arising in ≥ 2% of treated patients (adapted from [2]*)

	Nivolumab plus Ipilimumab (n = 313)		Nivolumab (n = 313)		Ipilimumab (n = 311)	
Side effects of treatment	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
All organ systems	300 (96%)	184 **(59%)**	270 (86%)	67 **(21%)**	268 (86%)	86 **(28%)**
Skin (rash, pruritus, vitiligo)	193 (62%)	20 (6%)	144 (46%)	7 (2%)	173 (56%)	9 (3%)
Gastrointestinal tract	150 (48%)	47 (15%)	70 (22%)	11 (4%)	117 (38%)	36 (12%)
Diarrhea	142 (45%)	29 (9%)	67 (21%)	9 (3%)	105 (34%)	18 (6%)
Colitis	40 (13%)	26 (8%)	7 (2%)	3 (1%)	35 (11%)	24 (8%)
Liver (transaminase elevation)	102 (33%)	62 (20%)	25 (8%)	9 (3%)	23 (7%)	5 (2%)
Endocrine organs	106 (34%)	20 (6%)	54 (17%)	5 (2%)	36 (12%)	8 (3%)
Hypothyroidism	53 (17%)	1 (<1%)	33 (11%)	0	14 (5%)	0
Hyperthyroidism	35 (11%)	3 (1%)	14 (4%)	0	3 (1%)	0
Adrenalitis	11 (4%)	6 (2%)	4 (1%)	2 (1%)	4 (1%)	1 (<1%)
Hypophysitis	23 (7%)	5 (2%)	2 (1%)	1 (<1%)	12 (4%)	5 (2%)
Pancreas (lipase/amylase elevation)	70 (22%)	43 (14%)	47 (15%)	20 (6%)	33 (11%)	16 (5%)
Lung (pneumonitis)	24 (8%)	3 (1%)	6 (2%)	1 (<1%)	6 (2%)	1 (<1%)
Kidney (creatinine elevation, nephritis)	22 (7%)	6 (2%)	4 (1%)	1 (<1%)	5 (2%)	1 (<1%)
Hypersensitivity/infusion reactions	13 (4%)	0	14 (4%)	1 (<1%)	8 (3%)	1 (<1%)

* The spectrum of side effects of pembrolizumab and their rates of occurrence are comparable to those of nivolumab. For pembrolizumab, however, no three-armed study is available comparing the incidence of side effects in the three modalities of treatment.

Treatment-associated deaths have been reported in the setting of both primary and adjuvant treatment *(Table 2)* (9–16).

The early initiation of corticosteroid treatment can shorten the duration of autoimmune side effects and prevent complications (e.g., intestinal perforation) (17). Algorithms for side-effect management, including recommended courses of action, are now available. Checkpoint inhibitors are no less effective in melanoma patients who stop taking them because of side effects (18–20). In 25% of patients treated with ipilimumab and nivolumab, side effects arose in more than one organ system (18). Thus, patients presenting with symptoms in one organ system must be carefully checked for side effects elsewhere (18, 21, 22). This article is based on information from pertinent publications retrieved by a literature search in PubMed and on an evaluation of a side-effect registry.

General considerations on monitoring

The management of a side effect is independent of the checkpoint inhibitor that caused it. These drugs all cause the same spectrum of side effects, but with differing frequencies *(Table 1)* (2, 3, 23). Anti-PD-L1 antibodies do not interrupt the interaction between PD-1 and PD-Ligand 2, but have similar side effects (24, 25).

Avelumab is the only checkpoint inhibitor that commonly causes infusion reactions (e.g., back pain, hypotension). Thus, according to the manufacturer's instructions, it should be given after premedication with acetaminophen and an antihistamine, at least for the first four infusions.

The cornerstones of side-effect management

The goals of side-effect management are

- to detect and diagnose side effects, including rare ones;
- to prevent severe and lethal side effects;
- to treat side effects appropriately and without delay;
- to interrupt, terminate, or continue anti-tumor therapy as appropriate;
- and to help patients deal optimally with the consequences of side effects.

Before starting treatment, patients should be explicitly informed that the efficacy of checkpoint inhibitors is not diminished even if they must be discontinued because of side effects. If they are not so informed, they might be disinclined to report side effects for fear of having to stop the treatment. The patient's family should also be present during informed consent discussions, as the endocrine or neurological side effects may result in a loss of drive or in personality changes that can hinder the patient's ability to seek help independently.

Monitoring during treatment

Patients should be monitored before treatment and at regular intervals during treatment, i.e., before every

cycle of monotherapy and once a week in patients receiving ipilimumab and nivolumab, clinical symptoms and laboratory abnormalities (electrolyte changes, transaminases, lipase/amylase, creatine kinase, thyroid function tests, creatinine, complete blood count and differential) *(Table 3)* (26). If a side effect is suspected, the origin of the symptoms should be investigated before the next administration of a checkpoint inhibitor.

Monitoring after the end of treatment

Side effects can also arise long after the termination of checkpoint-inhibitor therapy, as is shown by a reported case of paraplegia arising five months after the end of treatment with ipilimumab (27). The German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte,* BfArM) recommends the continuation of monitoring for at least five months after the last dose; we continue to monitor patients for up to two years after the last dose.

Organ systems

Gastrointestinal side effects

Colitis

Serious and life-threatening diarrhea and colitis occur most commonly under combination therapy with ipilimumab and nivolumab (15%) and much less commonly under anti-PD-1 therapy (1–4%) (1–4%) *(Table 1)* (2, 3, 28). The most serious such occurrences, involving intestinal perforation and death (<1%), were mainly described in earlier treatment studies (29, 30). Whenever a patient under checkpoint inhibitor therapy presents with gastrointestinal symptoms (26), the stool should be investigated for pathogens. In severe or therapy-refractory cases, cytomegalovirus (CMV) reactivation should be ruled out by CMV-PCR (PCR = polymerase chain reaction) in the serum and by colonoscopic biopsy with immunohistochemical CMV staining and CMV-PCR *(Table 3, eFigure a)* (31–34). The treatment is managed depending on severity according to the CTCAE classification. Gastrointestinal side effects of grade 3/4 require the prompt initiation of high-dose treatment with methylprednisolone at 1–2 mg/kg of body weight per day. In case of steroid resistance, or recurrence of the symptoms after reduction of the steroid dose, the neutralizing anti-tumor-necrosis-factor-α (TNF-α) antibody infliximab should be administered as well (26, 31, 35). If the symptoms persist for more than two weeks, parenteral nutrition is also recommended.

Hepatitis and pancreatitis

Severe or life-threatening autoimmune hepatitis arises in 20% of patients undergoing combination therapy, usually as an asymptomatic elevation of transaminases with or without elevation of the bilirubin concentration *(Table 1)* (2, 28, 36). Typically, no liver-specific autoantibodies are found (36, 37). Once infection and tumor progression have been ruled out *(Table 3),* immunosuppressive therapy with 1–2 mg/kg of methylprednisolone per day should be initiated. If there is no response, mycophenolate mofetil should be added on (26, 31, 35). Liver biopsy can be helpful in establishing the diagnosis and as a guide to further therapeutic decision-making (31, 36, 38). The successful administration of antithymocyte globulin has been described in cases refractory to glucocorticoids and mycophenolate mofetil (37, 39, 40). If hepatitis takes a persistent or severe course, other causes, such as CMV reactivation, should be ruled out once again (e1).

Asymptomatic elevations of lipase and amylase do not usually require treatment (2). If the problem becomes symptomatic, steroids can be given (31). Pancreatitis with and without ensuing pancreatic insufficiency has been described (9).

TABLE 2

Documented deaths due to side effects of checkpoint inhibitors (adapted from [e53])*

Organ system	Lethal side effect
Heart	myocarditis
	cardiomyopathy
	ventricular tachycardia
	cardiac arrest
Nervous system	Guillain-Barré syndrome
	myasthenia gravis
	encephalopathy
	paralysis
	neurological deterioration
Lungs	pneumonitis
	acute respiratory distress syndrome (ARDS)
Gastro-intestinal tract	colitis
	perforation
	hepatitis
Kidneys	renal failure
Skin	toxic epidermal necrolysis (TEN)
Endocrine	hypopituitarism
Other	hemolytic anemia
	bone-marrow aplasia
	angiopathy
	thromboembolism
	rhabdomyolysis

* According to the Paul Ehrlich Institute (PEI), 6.1% of reported complications are ultimately lethal (e35).

Endocrinopathies: thyroiditis, hypophysitis, and diabetes mellitus

Thyroid dysfunction and hypophysitis are among the more common endocrine side effects, arising mainly under combination therapy (28% and 7%, respectively) and anti-PD-1 antibody therapy (15% and 1%) *(Table 1)* (2). Adrenalitis is found in 1–4% of patients, diabetes

mellitus and diabetes insipidus in <1% (9, 26, 28, e2–e4). Under combination therapy, there is often more than one endocrine side effect at the same time (e5).

Endocrinopathies often have nonspecific symptoms, such as fatigue, weakness, dizziness, nausea/vomiting, anorexia, weight loss, headache, confusion, loss of libido, visual disturbances, abdominal pain, sweating, or tachycardia (31), and may thus be hard to differentiate from other causes, such as infection or progression of the underlying malignant disease *(Table 3)*.

Thyroiditis usually causes transient hyperthyroidism and subsequent hypothyroidism (28, e6). Hypophysitis *(eFigure b)*, which arises in 1–7% of patients, causes secondary adrenocortical insufficiency, presenting with fatigue, confusion, and electrolyte disturbances (2, e2, e3, e5). Adrenalitis with primary adrenocortical insufficiency can arise as well. Loss of the corticotropic axis leads to an Addison crisis presenting with dehydration, hypotension, and hyponatremia, and possibly with fever and abdominal pain. This is an emergency that calls for the immediate intravenous administration of glucocorticoids (26, 31, e2).

Cases of insulin-dependent diabetes mellitus have been reported (9, e4, e7–e11). Regular blood-sugar checks are recommended.

In addition to hormone-replacement therapy, symptom-oriented treatment and/or immunosuppression with glucocorticoids may be useful in some cases as well (26, 31, e12). In adrenocortical insufficiency, hormone-replacement therapy should be adjusted in situations that involve an elevated glucocorticoid requirement (infection/stress). The patient must be instructed accordingly and must be given an "emergency passport" (31). Checkpoint blockade can be continued under appropriate hormone replacement therapy.

Pulmonary side effects: pneumonitis

The incidence of pneumonitis in patients taking checkpoint inhibitors is 3–10%; this complication is lethal in 0.2–2% (18, e13–e15). The most common symptoms are dyspnea (53%), cough (35%), fever (12%), and chest pain (7%) (e14). One-third of patients are asymptomatic when pneumonitis is first diagnosed and are given the diagnosis upon a staging evaluation *(Figure a)* (e15). Chest x-rays fail to reveal pneumonitis in one-quarter of patients (e14). Checkpoint inhibitors should be temporarily discontinued, and methylprednisolone 1–2 mg/kg qd should be given, under antibiotic coverage if indicated. If this treatment fails, additional immune suppression with infliximab, mycophenolate mofetil, or cyclophosphamide is recommended (31). In most cases, checkpoint inhibition can be resumed (e14).

Manifestations resembling those of sarcoidosis, with central lymphadenopathy and potential involvement of other organs such as bone (e16–e19), can also be induced by checkpoint inhibitors and can present a differential diagnostic challenge.

Renal side effects

Renal function very often worsens under anti-PD-1 monotherapy (13–22%). Nephritis has been reported to arise in only 0.4–0.9% of cases (summary of product characteristics [www.fachinfo.de]; *Table 1*) (e20), but can manifest itself after a single infusion (e21). Renal failure has also been described as a complication of various checkpoint inhibitors (e22, e23). Renal side effects include tubulo-interstitial nephritis (16, e24–e26), glomerulonephritis (e27, e28), and thrombotic microangiopathy (e29). There have been rare case reports of lupus nephritis (e28) and possibly associated IgA nephropathy (e30).

Renal failure usually returns to baseline values under glucocorticoid therapy (26).

Cardiac side effects

Cardiac side effects including myocarditis, cardiomyopathy, and acute heart failure can take a lethal course (10, e31, e32), even in the adjuvant setting (29) *(Table 2)*. Thus, even minimal elevation of creatine kinase or troponin values or other clinical manifestations should prompt a cardiological evaluation *(Table 3)*. After the first case of cardiotoxicity with myocardial fibrosis was reported in 2013 in the context of a retrospective study of 752 patients treated with ipilimumab (16), anti-PD-1 therapy was also found to be associated with an elevated incidence of cardiotoxic side effects (5% versus 0% in the control group [manufacturer's information]). The cardiac complications of checkpoint inhibition can take many different forms, including heart failure, cardiomyopathy, conduction disorders, and myocarditis (11). Myocarditis, the most common cardiac complication (1%) (e33, e34), is often associated with myositis and myasthenia-like symptoms or rhabdomyolysis, and it is lethal in ca. 44–50% of cases (e35, e36). There have also been reports of checkpoint inhibition inducing pericarditis, pericardiac effusion and tamponade (22, e37, e38), intracardiac conduction disorders (e39), and cardiomyopathy with manifestations resembling takotsubo cardiomyopathy (e40).

Monitoring of all patients taking checkpoint inhibitors, including creatine kinase measurement and the meticulous evaluation of cardiac symptoms before each infusion, is essential. Corticosteroids given in conjunction with symptomatic treatment can save lives (e33, e41).

Musculoskeletal side effects

The musculoskeletal side effects include myositis, sometimes with cardiomyositis (e36). Myositis involving the diaphragm can present with dyspnea (e42). In checkpoint-inhibitor-induced myositis, autoantibodies are usually negative. Polymyalgia rheumatica and arthritis arise in 6–11% of patients (26, e43, e44) and can take a severe course leading to physical deformity (e45). There have been documented cases of rhabdomyolysis (21, e46, e47), dermatomyositis (e48), eosinophilic fasciitis (e44), tenosynovitis (e49), and

TABLE 3

Monitoring and diagnostic testing under treatment with checkpoint inhibitors (26, 28, 31, e72)

Generally recommended laboratory tests before and after treatment:		
Baseline[*1]	CBC/diff, Na, K, Ca, creatinine, CK, troponin, bilirubin, liver enzymes (AST, ALT, GGT), LDH, amylase, lipase, glucose, TSH, fT4, CRP when indicated, BUN; HIV, hepatitis A, B, C and (when indicated) CMV and EBV serology; quantiferon test when indicated, fasting cortisol when indicated	
Before each cycle or once a week [*1, *2]	CBC/diff, Na, K, Ca, creatinine, CK, bilirubin, liver enzymes (AST, ALT, GGT), LDH, amylase, lipase, glucose, TSH, fT4	
In case of side effects	**Diagnostic testing**	**Treatment**
Diarrhea/colitis	**general:** stool for pathogens; calprotectin in stool if indicated **in case of a severe or refractory course:** colonoscopy or rectosigmoidoscopy with biopsy (including staining for CMV); CMV-PCR abdominal plain film (to rule out free air due to perforation); abdominal CT if indicated	**general:** rehydration; methylprednisolone 1–2 mg/kg/d **in case of a severe or refractory course:** infliximab 5 mg/kg i. v.
Hepatitis	**general:** rule out viral infection, viral reactivation, or vascular cause; upper abdominal ultrasonography; if indicated, abdominal CT or liver MRI to rule out progression **in case of a severe or refractory course:** liver biopsy with CMV- and EBV-PCR	**general:** methylprednisolone 1–2 mg/kg/d **in case of a severe or refractory course:** mycophenolate mofetil 1–2 g/d; if unsuccessful, anti-thymocyte-globulin (ATG) or tacrolimus
Pancreatitis	upper abdominal ultrasonography; if indicated, CT/MRI or magnetic resonance cholangio-pancreatigraphy (MRCP)	**symptomatic course:** methylprednisolone 1 mg/kg/d
Endocrinopathy	**Thyroiditis:** fT4, TSH, TPO-AB, TSH-receptor-AB; where indicated, thyroid scintigraphy or ultrasonography **Hypophysitis:** TSH, fT4, ACTH, LH, FSH, prolactin, IGF-1, estradiol, testosterone, SHBG cortisol 8:00 am; if indicated, head MRI with sella cuts	**general:** for hypothyroidism: hormone substitution with thyroxine symptomatic courses: beta-blockers **general:** hormone substitution with hydrocortisone (e.g., 20 mg-10 mg-0); testosterone and thyroxine as indicated
Pneumonitis	**general:** thoracic CT, pulmonary function tests **in case of a severe or refractory course:** bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy if indicated	**general:** methylprednisolone 1 mg/kg/d; antibiotics if indicated **in case of a severe or refractory course:** infliximab 5 mg/kg i. v. or mycophenolate mofetil 1–2 g/d or cyclophosphamide; oxygen
Renal side effects	urinalysis and culture, urine microprotein analysis; 24-hour urine collection renal biopsy as indicated	**general:** methylprednisolone 1 mg/kg/d
Cardiac side effects	CK, troponin, pro-BNP, myoglobin EKG, echocardiography coronary angiography; cardiac PET-MRT myocardial biopsy as indicated	**general:** methylprednisolone 1 mg/kg/d symptomatic course: intensive care as needed **in case of a severe or refractory course:** unclear
Musculoskeletal side effects	**Myositis:** CK, troponin, myoglobin, K, Ca, uric acid, muscle biopsy as indicated, rule out cardiomyositis **Arthritis/rheumatic disease/temporal arteritis:** ANA, ENA, dsDNA-AB, CCP-AB, RF, clinical examination of the joints, ultrasonography of the temporal artery, ultrasonography or MRI of affected joints and tendons	**general:** glucocorticoids 1 mg/kg/d **severe or recurrent arthritis:** methotrexate or TNF-α inhibitors **recurrent temporal arteritis:** tocilizumab
Neurological side effects	neurological examination CSF examination; head MRI EEG, EMG, NCV	**general:** methylprednisolone 1 mg/kg/d **in case of a severe or refractory course:** if indicated, methylprednisolone 1 g qd x 3–5 d (e120)

[*1] according to the authors' experience; [*2] under combination therapy (Nivo+Ipi)

ACTH: adrenocorticotrophic hormone; AB, antibody; ALT: alanine aminotransferase; ANA: antinuclear antibody; AST: aspartate aminotransferase; Ca: calcium; CBC/diff: complete blood count with differential; CCP-AB: cyclic citrulline peptide antibody; CK: creatine kinase; CMV: cytomegalovirus; CRP: C-reactive protein; CSF, cerebrospinal fluid; CT: computerized tomography; d: day(s); dsDNA-AB: double-stranded DNA antibody; EBV: Epstein-Barr virus; EEG: electroencephalography; EKG: electrocardiogram; EMG: electromyography; ENA: extractable nuclear antibody; FSH: follicle-stimulating hormone; fT4: free T4; GGT: gamma-glutamyl transferase; HIV: human immunodeficiency virus; IGF-1: insulin-like growth factor-1; K: potassium; LDH: lactate dehydrogenase; LH: luteinizing hormone; MRI: magnetic resonance imaging; Na: sodium; NCV: nerve conduction velocities; PCR: polymerase chain reaction; PET: positrone-emission tomography; pro-BNP: pro brain natriuretic peptide; qd: per day; RF: rheumatoid factor; SHBG: sex-hormone-binding globulin; TNF: tumor necrosis factor; TPO-AB: thyroid peroxidase antibody; TSH: thyroid-stimulating hormone

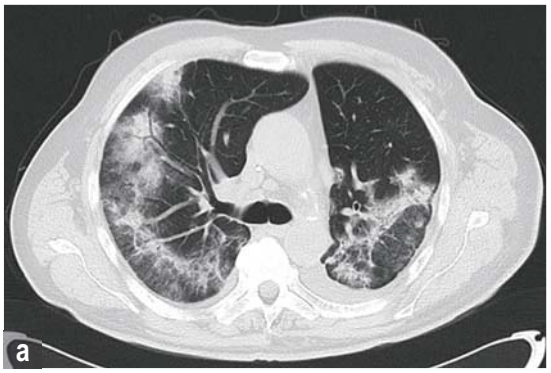


Figure: Pneumonitis (a), leukotrichia (b)

a) Typical ground-glass opacity in the chest x-ray of a patient with pneumonitis. Cough, fever, and exhaustion arose after one infusion of pembrolizumab.

b) Leukotrichia of the eyebrows and lashes in a 62-year-old man after combined treatment with ipilimumab and the anti-PD-1 antibody nivolumab.

giant cell arteritis (e50). The treatment is with glucocorticoids, possibly supplemented by immune-modulating drugs such as methotrexate or biological agents such as the interleukin-6 receptor antibody tocilizumab (e51).

Neurological side effects

Neurological side effects arise in 1–5% of patients (13, 16, 31, e52) and carry high morbidity with damaging sequelae (13) and significant mortality; these include Guillain-Barré syndrome (29), encephalopathy, and paralysis *(Table 2)* (e53). Symptoms such as headache, dizziness, apathy, ataxia, tremor, weakness, aphasia, memory impairment, and impaired wakefulness call for neurological evaluation *(Table 3)*.

Side effects involving the central nervous system (CNS) include encephalopathy (e54–e61), granulomatous CNS inflammation (16), limbic encephalitis (e62), non-infectious meningitis (e63), Tolosa-Hunt syndrome (16), and transverse myelitis (e64). Focal seizures and epilepsy can arise (e65) and may be followed by Parkinson-like bradykinesia (13). There have also been reports of dysgeusia and hypogeusia, insomnia and hypersomnia, lethargy, memory impairment, and vertigo. A case of myelopathy causing paraplegia has been reported (e66). In another case, checkpoint-inhibitor-induced brainstem encephalopathy led to death within one week (12).

The reported side effects involving the peripheral nerves include peripheral neuropathies (among them facial palsy and abducens palsy) (e67, e68), chronic inflammatory demyelinating polyneuropathy (e64), meningoradiculoneuritis, enteric neuropathy and necrotic myelopathy (e66), demyelination (e69), hyperesthesia, neuralgia, and optic neuritis.

Myasthenia gravis that has been induced or exacerbated by checkpoint inhibitors is lethal in one-third of cases (e70). Antibodies against acetylcholine are only rarely found. Systemic diseases such as sarcoidosis can also have neurological manifestations (e71).

Glucocorticoid administration can improve the neurological manifestations (13, e72). Further treatments include intravenous immunoglobulins (IVIG), plasmapheresis, and/or the costimulation inhibitor abatacept (13, e73). The differential diagnosis encompasses brain metastases, ischemia, and infection, as well as endocrinopathies, which should be particularly borne in mind as a potential cause of personality changes.

Side effects on the skin and eyes

Cutaneous reactions arise in 46–62% of patients but are mild more than 90% of the time (e74, e75) and can be treated with topical emollients and glucocorticoid-containing ointments (e76). Severe cutaneous side effects arise in 2–6% of patients and include drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, toxic epidermal necrolysis, and bullous changes such as bullous pemphigoid (e77–e80) and herpetiform dermatitis (e81). Problems of the latter type require dermatological evaluation, including immunofluorescence (e82). Leukotrichia is a further side effect *(Figure b)*.

Lichenoid skin reactions, sometimes with mucosal involvement, arise in 17–22% of patients (e82, e83). Moreover, psoriasiform skin changes can be induced, or pre-existing psoriasis or psoriatic arthritis exacerbated (e84–e86). There have also been reports of Grover's disease, reactions resembling chronic lichenoid pityriasis, dermatomyositis, and panniculitis resembling erythema nodosum (e48, e87–e90).

Autoimmune side effects involving the eyes include blindness (e23), anterior uveitis (e91, e92), sicca syndrome (e45, e93), ischemia or neuritis of the optic nerve, and temporal arteritis (e50, e94).

Hematological and other side effects

Hematological side effects include anemia (2.8%) (e95, e96), thrombocytopenia (1.2%) (e97, e98), leukopenia (0.5%), lymphopenia (6.4%), and neutropenia (0.7%) (26, e99). Blood-count alterations such as pancytopenia and agranulocytosis (e100) can be very dangerous (e35) *(Table 2)*. In 43% of fully documented cases, the associated refractory autoimmune hemolytic anemia took a lethal course (e35). Acquired hemophilia after treatment with ipilimumab has been reported as well (e101). Glucocorticoid therapy can be effective (e102), as can the administration of granulocyte colony stimulating factor (GCSF).

Infusion reactions arise mainly with avelumab (17%) and less commonly with other checkpoint inhibitors (4%) *(Table 1)*.

General considerations of management

Treatment

Most side effects can be adequately treated by the prompt administration of glucocorticoids (methylprednisolone, 1–2 mg/kg of body weight per day; taper over 28 days). Prolonged glucocorticoid therapy can cause adrenocortical insufficiency and other problems.

Endocrine side effects require hormone replacement therapy, usually for life (e12). It is unclear whether high-dose glucocorticoid therapy helps maintain hormonal function. With respect to hypophysitis, at least, this seems not to be the case (e12).

If the side effects fail to respond to glucocorticoids in 3–4 days, the immune suppression should be escalated without delay. If the addition of a second immunosuppressive agent fails to achieve a response, or is followed by a protracted or complicated clinical course, then there should be a repeated evaluation to rule out infection (34, e103).

Recurrent side effects (re-exposure)

The repeated administration of checkpoint-inhibitor therapy in a patient who previously experienced side effects should be discussed with the patient in relation to the following factors:

- the severity of the side effect and the likelihood that it will recur;
- the extent of the malignant disease and the probability of it leading to death;
- the availability, if any, of effective alternative treatments.

A history of life-threatening side effects is a contraindication to the reintroduction of immunotherapy (5). The reintroduction of anti-PD-1 therapy induces side effects once again in ca. 25% of patients (19, e14). Exacerbations of cardiomyositis, thrombocytopenia, and bullous skin diseases after re-exposure have been reported (e32, e80, e104).

Special pre-existing illnesses

Pre-existing autoimmune disease does not in itself contraindicate checkpoint-inhibition therapy (5). Among patients with pre-existing autoimmune disease who underwent checkpoint-inhibition therapy, 32–33% had a tumor response (e105, e106), while 38–42% of those receiving anti-PD-1 therapy (e105, e106) and 27% of those receiving anti-CTLA-4 therapy experienced a reactivation of their autoimmune disease (e107). Rheumatological diseases were the most likely to be exacerbated (>50%) (e105, e106); exacerbations of multiple sclerosis and myasthenia gravis have also been described (e70, e108).

In transplant patients, too, immunotherapy can lead to tumor response despite immune suppression (e109), but it can also induce rejection reactions (5). These are reportedly common under anti-PD-1 therapy, while ipilimumab was not associated with a single rejection reaction in five organ transplant recipients (two patients each with kidney and liver transplants, one with a heart transplant) (e109, e110).

Key messages

- Before any treatment with checkpoint inhibitors is initiated, the patient and family must be thoroughly informed of the side effects, complications, and rules of conduct. All other physicians caring for the patient must also be correspondingly informed and must be given contact data for the treating personnel in the oncological center.
- In addition to the commonly recognized side effects, including autoimmune colitis and hepatitis, cutaneous lesions, endocrinopathies (thyroiditis, hypophysitis, diabetes mellitus), and pneumonitis, 1–5% of patients treated with checkpoint inhibitors have cardiac side effects (myocarditis) and another 1–5% have neurological side effects.
- Interdisciplinary collaboration is highly recommended, particularly when the patient manifests severe and/or intractable side effects or suffers from certain special conditions (e.g., autoimmune disease or status post transplantation).
- The rapid diagnosis and appropriate treatment of side effects can lower morbidity and mortality.
- Structured side-effect registries, sharing of experience, and interdisciplinary collaboration can lead to improved treatment concepts and to the identification of risk factors for the appearance of side effects.

Anti-PD-1 therapy, in one study, caused rejection reactions (some of them fatal) in 46% of patients who had received liver transplants (e111–e113). Rejection reactions have also been described in 38% of patients who had received renal transplants (e109, e112, e114–e116). One heart-transplant recipient did not have a rejection reaction under anti-PD-1 therapy (e109).

Patients with chronic hepatitis B/C or HIV also showed a tumor response to anti-PD-1 therapy without any elevated frequency of side effects or virus activation (e112, e117–e119).

Discussion

Patients with complex side effects or relevant pre-existing diseases should be treated in an experienced center. If the side effects are refractory to treatment with glucocorticoids, the immunosuppression should be further escalated (after a repeated diagnostic evaluation, if indicated). Side-effect documentation in clinical studies needs to be improved: cases with a fatal outcome must be specifically documented, rather than being subsumed under "side effects of grade 3 or above"; side effects must be documented even if they arise in less than 5% of patients; and the percentage of patients who suffer permanent harm from side effects must be stated. The structured documentation of rare side effects, and of side effects in special patient groups, may aid in the identification of risk factors. An online side-effect registry for this purpose is now being created in collaboration with the Paul Ehrlich Institute.

Acknowledgement
We thank Prof. Dagmar Führer for her critical review of the manuscript.

Conflict of interest statement
Prof. Heinzerling has served as a paid consultant for BMS, MSD, Roche, Novartis, Amgen, Curevac, Pierre Fabre, and Sanofi. She has received reimbursement of meeting attendance fees and travel expenses from BMS, Novartis, Roche, and Amgen and lecture honoraria from BMS, Amgen, MSD, Roche, and Novartis. She has received third-party funding for scientific research from Novartis, Curevac, BMS, MSD, Amgen, and Roche.

PD Dr. De Toni has served as a paid consultant for AstraZeneca, Bayer, BMS, EISAI, Eli Lilly & Co, Pfizer, IPSE, and Roche. He has received reimbursement of meeting attendance fees and travel expenses from Arqule, BMS, Bayer, and Celsion and lecture honoraria from BMS and Falk. He has received third-party funding for scientific research from Arqule, AstraZeneca, BMS, Bayer, Eli Lilly, and Roche.

PD Dr. Zimmer has served as a paid consultant for BMS, Novartis, Sanofi, Pierre Fabre, Roche, and MSD. She has received reimbursement of meeting attendance fees and travel expenses from Novartis, BMS, Pierre Fabre, MSD und Amgen amd lecture honoraria from BMS, Novartis, Pierre Fabre, Roche, and MSD.

The other authors state that they have no conflict of interest.

Manuscript submitted on 5 May 2018, revised version accepted on 6 December 2018.

Translated from the original German by Ethan Taub, M.D.

References

1. Overman MJ, McDermott R, Leach JL, et al.: Nivolumab in patients with metastatic DNA mismatch repair deficient/microsatellite instability–high colorectal cancer (CheckMate 142): results of an open-label, multicentre, phase 2 study. Lancet Oncol 2017; 18: 1182–91.
2. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al.: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017; 377: 1345–56.
3. Schachter J, Ribas A, Long GV, et al.: Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017; 390: 1853–62.
4. Long GV, Atkinson V, Cebon JS, et al.: Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. Lancet Oncol 2017; 18: 1202–10.
5. Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378: 158–68.
6. Iwama S, De RA, Callahan MK, Slovin SF, Wolchok JD, Caturegli P: Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med 2014; 6: 230ra45.
7. Dubin K, Callahan MK, Ren B, et al.: Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun 2016; 7: 10391.
8. Chaput N, Lepage P, Coutzac C, et al.: Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol 2017; 28: 1368–79.
9. Hofmann L, Forschner A, Loquai C, et al.: Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016; 60: 190–209.
10. Johnson DB, Balko JM, Compton ML, et al.: Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016; 375: 1749–55.
11. Heinzerling L, Ott PA, Hodi FS, et al.: Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer 2016; 4: 50.
12. Bossart S, Thurneysen S, Rushing E, et al.: Case report: encephalitis, with brainstem involvement, following checkpoint inhibitor therapy in metastatic melanoma. Oncologist 2017, 22: 749–53.
13. Zimmer L, Goldinger SM, Hofmann L, et al.: Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer 2016; 60: 210–25.
14. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS: Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol 2016; 2: 1607–16.
15. Hamid O, Robert C, Daud A, et al.: Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013; 369: 134–44.
16. Voskens CJ, Goldinger SM, Loquai C, et al.: The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. PLoS One 2013; 8: e53745.
17. O'Day S, Weber JS, Wolchok JD, et al.: Effectiveness of treatment guidance on diarrhea and colitis across ipilimumab studies. J Clin Oncol 2011; 29: 15-suppl 8554.
18. Schadendorf D, Wolchok JD, Hodi FS, et al.: Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse avents: a pooled analysis of randomized phase II and III trials. J Clin Oncol 2017; 35: 3807–14.
19. Santini FC, Rizvi H, Wilkins O, et al.: Safety of retreatment with immunotherapy after immune-related toxicity in patients with lung cancers treated with anti-PD(L)-1 therapy. J Clin Oncol 2017; 35: 15_suppl 9012.
20. Horvat TZ, Adel NG, Dang TO, et al.: Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol 2015; 33: 3193–8.
21. Bilen MA, Subudhi SK, Gao J, Tannir NM, Tu SM, Sharma P: Acute rhabdomyolysis with severe polymyositis following ipilimumab-nivolumab treatment in a cancer patient with elevated anti-striated muscle antibody. J Immunother Cancer 2016; 4: 36.
22. Dasanu CA, Jen T, Skulski R: Late-onset pericardial tamponade, bilateral pleural effusions and recurrent immune monoarthritis induced by ipilimumab use for metastatic melanoma. J Oncol Pharm Pract 2017; 23: 231–4.
23. Weber JS, D'Angelo SP, Minor D, et al.: Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16: 375–84.
24. Rittmeyer A, Barlesi F, Waterkamp D, et al.: Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017; 389: 255–65.
25. Barlesi F, Vansteenkiste J, Spigel D, et al.: Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol 2018; 19: 1468–79.
26. Hassel JC, Heinzerling L, Aberle J, et al.: Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): evaluation and management of adverse drug reactions. Cancer Treat Rev 2017; 57: 36–49.
27. O'Kane GM, Lyons TG, Colleran GC, et al.: Late-onset paraplegia after complete response to two cycles of ipilimumab for metastatic melanoma. Oncol Res Treat 2014; 37: 757–60.
28. Spain L, Diem S, Larkin J: Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev 2016; 44: 51–60.
29. Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al.: Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med 2016; 375: 1845–55.
30. Tarhini AA, Lee SJ, Hodi FS, et al.: A phase III randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma (U.S. Intergroup E1609): preliminary safety and efficacy of the ipilimumab arms. J Clin Oncol 2017; 35: 15_suppl 9500.
31. Brahmer JR, Lacchetti C, Schneider BJ, et al.: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018; 36: 1714–68.
32. Geukes Foppen MH, Rozeman EA, van Wilpe S, et al.: Immune checkpoint inhibition-related colitis: symptoms, endoscopic features, histology and response to management. ESMO open 2018; 3: e000278.
33. Hundorfean G, Atreya R, Agaimy A, et al.: Fluorescein-guided confocal laser endomicroscopy for the detection of ipilimumab-induced colitis. Endoscopy 2012; 44: E78–9.
34. Lankes K, Hundorfean G, Harrer T, et al.: Anti-TNF-refractory colitis after checkpoint inhibitor therapy: possible role of CMV-mediated immunopathogenesis. Oncoimmunology 2016; 5: e1128611.
35. Haanen JBAG, Carbonnel F, Robert C, et al.: Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (Suppl_4): iv119–42.
36. de Martin E, Michot JM, Papouin B, et al.: Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018; 68: 1181–90.
37. Spänkuch I, Gassenmaier M, Tampouri I, et al.: Severe hepatitis under combined immunotherapy: resolution under corticosteroids plus anti-thymocyte immunoglobulins. Eur J Cancer 2017; 81: 203–5.
38. Doherty GJ, Duckworth AM, Davies SE, et al.: Severe steroid-resistant anti-PD1 T-cell checkpoint inhibitor-induced hepatotoxicity driven by biliary injury. ESMO Open 2017; 2: e000268.
39. Chmiel KD, Suan D, Liddle C, et al.: Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy. J Clin Oncol 2011; 29: e237–40.
40. McGuire HM, Shklovskaya E, Edwards J, et al.: Anti-PD-1-induced high-grade hepatitis associated with corticosteroid-resistant T cells: a case report. Cancer Immunol Immunother 2018; 67: 563–73.

Corresponding author
Prof. Dr. med. Lucie Heinzerling, MPH
Hautklinik, Universitätsklinikum Erlangen
Ulmenweg 18, 91054 Erlangen, Germany
Lucie.Heinzerling@uk-erlangen.de

► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref08119

eFigure, eTable:
www.aerzteblatt-international.de/19m0119

Supplementary material to:

Checkpoint Inhibitors

The Diagnosis and Treatment of Side Effects

by Lucie Heinzerling, Enrico N. de Toni, Georg Schett, Gheorghe Hundorfean, and Lisa Zimmer

Dtsch Arztebl Int 2019; 116: 119–26. DOI: 10.3238/arztebl.2019.0119

eReferences

e1. Uslu U, Agaimy A, Hundorfean G, Harrer T, Schuler G, Heinzerling L: Autoimmune colitis and subsequent CMV-induced hepatitis after treatment with ipilimumab. J Immunother 2015; 38: 212–5.

e2. Eigentler TK, Hassel JC, Berking C, et al.: Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev 2016; 45: 7–18.

e3. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al.: Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol 2018; 4: 173–82.

e4. Changizzadeh PN, Mukkamalla SKR, Armenio VA: Combined checkpoint inhibitor therapy causing diabetic ketoacidosis in metastatic melanoma. J Immunother Cancer 2017; 5: 97.

e5. Scott ES, Long GV, Guminski A, Clifton-Bligh RJ, Menzies AM, Tsang VH: The spectrum, incidence, kinetics and management of endocrinopathies with immune checkpoint inhibitors for metastatic melanoma. Eur J Endocrinol 2018; 178: 175–82.

e6. Lee H, Hodi FS, Giobbie-Hurder A, et al.: Characterization of thyroid disorders in patients receiving immune checkpoint inhibition therapy. Cancer Immunol Res 2017; 5: 1133–40.

e7. Hughes J, Vudattu N, Sznol M, et al.: Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care 2015; 38: e55–7.

e8. Martin-Liberal J, Furness AJS, Joshi K, Peggs KS, Quezada SA, Larkin J: Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. Cancer Immunol Immunother 2015; 64: 765–7.

e9. Okamoto M, Okamoto M, Gotoh K, et al.: Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. J Diabetes Investig 2016; 7: 915–8.

e10. Gaudy C, Clévy Ć, Monestier S, et al.: Anti-PD1 pembrolizumab can induce exceptional fulminant type 1 diabetes. Diabetes Care 2015; 38: e182–3.

e11. Miyoshi Y, Ogawa O, Oyama Y: Nivolumab, an anti-programmed cell death-1 antibody, induces fulminant type 1 diabetes. Tohoku J Exp Med 2016; 239: 155–8.

e12. Min L, Hodi FS, Giobbie-Hurder A, et al.: Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study. Clin Cancer Res 2015; 21: 749–55.

e13. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS: Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol 2016; 2: 1607–16.

e14. Naidoo J, Wang X, Woo KM, et al.: Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol 2017; 35: 709–17.

e15. Nishino M, Ramaiya NH, Awad MM, et al.: PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. Clin Cancer Res 2016; 22: 6051–60.

e16. Firwana B, Ravilla R, Raval M, Hutchins L, Mahmoud F: Sarcoidosis-like syndrome and lymphadenopathy due to checkpoint inhibitors. J Oncol Pharm Pract 2017; 23: 620–4.

e17. Montaudié H, Pradelli J, Passeron T, Lacour JP, Leroy S: Pulmonary sarcoid-like granulomatosis induced by nivolumab. Br J Dermatol 2016; 176: 1060–3.

e18. Suozzi KC, Stahl M, Ko CJ, et al.: Immune-related sarcoidosis observed in combination ipilimumab and nivolumab therapy. JAAD Case Rep 2016; 2: 264–8.

e19. Jespersen H, Bjursten S, Ny L, Levin M: Checkpoint inhibitor-induced sarcoid reaction mimicking bone metastases. Lancet Oncol 2018; 19: e327.

e20. Boutros C, Tarhini A, Routier E, et al.: Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016; 13: 473–86.

e21. Vandiver JW, Singer Z, Harshberger C: Severe hyponatremia and immune nephritis following an initial infusion of nivolumab. Target Oncol 2016; 11: 553–6.

e22. Rizvi NA, Hellmann MD, Brahmer JR, et al.: Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2016; 34: 2969–79.

e23. Voskens C, Cavallaro A, Erdmann M, et al.: Anti-cytotoxic T-cell lymphocyte antigen-4-induced regression of spinal cord metastases in association with renal failure, atypical pneumonia, vision loss, and hearing loss. J Clin Oncol 2012; 30: e356–7.

e24. Kaufman HL, Russell J, Hamid O, et al.: Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016; 17: 1374–85.

e25. Escandon J, Peacock S, Trabolsi A, Thomas DB, Layka A, Lutzky J: Interstitial nephritis in melanoma patients secondary to PD-1 checkpoint inhibitor. J Immunother Cancer 2017; 5: 3.

e26. Shirali AC, Perazella MA, Gettinger S: Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. Am J Kidney Dis 2016; 68: 287–91.

e27. Jung K, Zeng X, Bilusic M: Nivolumab-associated acute glomerulonephritis: a case report and literature review. BMC Nephrol 2016; 17: 188.

e28. Fadel F, Karoui K El, Knebelmann B: Anti-CTLA4 antibody-induced lupus nephritis. N Engl J Med 2009; 361: 211–2.

e29. Cortazar FB, Marrone KA, Troxell ML, et al.: Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int 2016; 90: 638–47.

e30. Kishi S, Minato M, Saijo A, et al.: IgA nephropathy after nivolumab therapy for postoperative recurrence of lung squamous cell carcinoma. Intern Med 2018; 57: 1259–63.

e31. Läubli H, Balmelli C, Bossard M, Pfister O, Glatz K, Zippelius A: Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. J Immunother Cancer 2015; 3: 11.

e32. Tajmir-Riahi A, Bergmann T, Schmid M, Agaimy A, Schuler G, Heinzerling L: Life-threatening autoimmune cardiomyopathy reproducibly induced in a patient by checkpoint inhibitor therapy. J Immunother 2018; 41: 35–8.

e33. Mahmood SS, Fradley MG, Cohen JV, et al.: Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol 2018; 71: 1755–64.

e34. Semper H, Muehlberg F, Schulz-Menger J, Allewelt M, Grohé C: Drug-induced myocarditis after nivolumab treatment in a patient with PDL1-negative squamous cell carcinoma of the lung. Lung Cancer 2016; 99: 117–9.

e35. Heymans L, Mentzer D, Keller-Stanislawski B: Verdachtsfälle unerwünschter Reaktionen nach Checkpoint-Inhibitoren aus Deutschland. Bull Arzneimittelsicherheit 2016; 4: 11–8.

e36. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB: Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet 2018; 391: 933.

e37. Yun S, Vincelette ND, Mansour I, Hariri D, Motamed S: Late onset ipilimumab-induced pericarditis and pericardial effusion: a rare but life threatening complication. Case Rep Oncol Med 2015; Article ID: 794842.

e38. Kushnir I, Wolf I: Nivolumab-induced pericardial tamponade: a case report and discussion. Cardiology 2017; 136: 49–51.

e39. Gibson R, Delaune J, Szady A, Markham M: Suspected autoimmune myocarditis and cardiac conduction abnormalities with nivolumab therapy for non-small cell lung cancer. BMJ Case Rep 2016; 2016. pii: bcr2016216228.

e40. Geisler BP, Raad RA, Esaian D, Sharon E, Schwartz DR: Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: a case of takotsubo-like syndrome. J Immunother Cancer 2015; 3: 4.

e41. Arangalage D, Delyon J, Lermuzeaux M, et al.: Survival after fulminant myocarditis induced by immune-checkpoint inhibitors. Ann Intern Med 2017; 167: 683–4.

e42. John S, Antonia SJ, Rose TA, et al.: Progressive hypoventilation due to mixed $CD8^+$ and $CD4^+$ lymphocytic polymyositis following tremelimumab - durvalumab treatment. J Immunother Cancer 2017; 5: 54.

e43. Belkhir R, Burel SL, Dunogeant L, et al.: Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. Ann Rheum Dis 2017; 76: 1747–50.

e44. Lidar M, Giat E, Garelick D, et al.: Rheumatic manifestations among cancer patients treated with immune checkpoint inhibitors. Autoimmun Rev 2018; 17: 284–9.

e45. de Velasco G, Bermas B, Choueiri TK: Autoimmune arthropathy and uveitis as complications of programmed death 1 inhibitor treatment. Arthritis Rheumatol 2016; 68: 556–7.

e46. Chen Q, Huang DS, Zhang LW, Li YQ, Wang HW, Liu HB: Fatal myocarditis and rhabdomyolysis induced by nivolumab during the treatment of type B3 thymoma. Clin Toxicol (Phila) 2018; 56: 667–71.

e47. Sakai K, Mochizuki H, Mochida K, Shiomi K, Amano M, Nakazato M: A case of nivolumab-induced severe mononeuropathy multiplex and rhabdomyolysis. Case Rep Med 2017; Article ID:1093858.

e48. Sheik Ali S, Goddard AL, Luke JJ, et al.: Drug-associated dermatomyositis following ipilimumab therapy: a novel immune-mediated adverse event associated with cytotoxic T-lymphocyte antigen 4 blockade. JAMA Dermatology 2015; 151: 195–9.

e49. Chan MMK, Kefford RF, Carlino M, Clements A, Manolios N: Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. J Immunother 2015; 38: 37–9.

e50. Goldstein BL, Gedmintas L, Todd DJ: Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of ctla-4. Arthritis Rheumatol 2014; 66: 768–9.

e51. Kim ST, Tayar J, Trinh VA, et al.: Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. Ann Rheum Dis 2017; 76: 2061–4.

e52. Cuzzubbo S, Javeri F, Tissier M, et al.: Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. Eur J Cancer 2017; 73: 1–8.

e53. Heinzerling L, Goldinger SM: A review of serious adverse effects under treatment with checkpoint inhibitors. Curr Opin Oncol 2017; 29: 136–44.

e54. Conry RM, Sullivan JC, Nabors LB III:. Ipilimumab-induced encephalopathy with a reversible splenial lesion. Cancer Immunol Res 2015; 3: 598–601.

e55. Carl D, Grullich C, Hering S, Schabet M: Steroid responsive encephalopathy associated with autoimmune thyroiditis following ipilimumab therapy: a case report. BMC Res Notes 2015; 8: 316.

e56. Stein MK, Summers BB, Wong CA, Box HL, Cleveland KO: Meningoencephalitis following ipilimumab administration in metastatic melanoma. Am J Med Sci 2015; 350: 512–3.

e57. Williams TJ, Benavides DR, Patrice KA, et al.: Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. JAMA Neurol 2016; 73: 928–33.

e58. Tchapyjnikov D, Borst AJ: Immune-related neurological symptoms in an adolescent patient receiving the checkpoint inhibitor nivolumab. J Immunother 2017; 40: 286–8.

e59. Larkin J, Chmielowski B, Lao CD, et al.: Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in advanced melanoma, including a case series of encephalitis. Oncologist 2017; 22: 709–18.

e60. Schneider S, Potthast S, Komminoth P, Schwegler G, Böhm S: PD-1 checkpoint inhibitor associated autoimmune encephalitis. Case Rep Oncol 2017; 10: 473–8.

e61. Leitinger M, Varosanec MV, Pikija S, et al.: Fatal necrotizing encephalopathy after treatment with nivolumab for squamous non-small cell lung cancer: case report and review of the literature. Front Immunol 2018; 9: 108.

e62. Salam S, Lavin T, Turan A: Limbic encephalitis following immunotherapy against metastatic malignant melanoma. BMJ Case Rep 2016; 2016, pii: bcr2016215012.

e63. Yang JC, Hughes M, Kammula U, et al.: Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother 2007; 30: 825–30.

e64. Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S: Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. Neuro Oncol 2014; 16: 589–93.

e65. Mandel JJ, Olar A, Aldape KD, Tremont-Lukats IW: Lambrolizumab induced central nervous system (CNS) toxicity. J Neurol Sci 2014; 344: 229–31.

e66. Abdallah AO, Herlopian A, Ravilla R, et al.: Ipilimumab-induced necrotic myelopathy in a patient with metastatic melanoma: a case report and review of literature. J Oncol Pharm Pract 2016; 22: 537–42.

e67. Tarhini A: Immune-mediated adverse events associated with ipilimumab CTLA-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica (Cairo) 2013; 2013: 857519.

e68. Thaipisuttikul I, Chapman P, Avila EK: Peripheral neuropathy associated with ipilimumab: a report of 2 cases. J Immunother 2015; 38: 77–9.

e69. Maurice C, Schneider R, Kiehl TR, et al.: Subacute CNS demyelination after treatment with nivolumab for melanoma. Cancer Immunol Res 2015; 3: 1299–302.

e70. Makarious D, Horwood K, Coward JIG: Myasthenia gravis: an emerging toxicity of immune checkpoint inhibitors. Eur J Cancer 2017; 82: 128–36.

e71. Murphy KP, Kennedy MP, Barry JE, O'Regan KN, Power DG: New-onset mediastinal and central nervous system sarcoidosis in a patient with metastatic melanoma undergoing CTLA4 monoclonal antibody treatment. Oncol Res Treat 2014; 37: 351–3.

e72. Spain L, Walls G, Julve M, et al.: Neurotoxicity from immune-checkpoint inhibition in the treatment of melanoma: a single centre experience and review of the literature. Ann Oncol 2017; 28: 377–85.

e73. Kumar B, Ballas Z: Adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378: 1164.

e74. Belum VR, Benhuri B, Postow MA, et al.: Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer 2016; 60: 12–25.

e75. Sibaud V, Meyer N, Lamant L, Vigarios E, Mazieres J, Delord JP: Dermatologic complications of anti-PD-1/PD-L1 immune checkpoint antibodies. Curr Opin Oncol 2016; 28: 254–63.

e76. Abdel-Rahman O, El Halawani H, Fouad M: Risk of cutaneous toxicities in patients with solid tumors treated with immune checkpoint inhibitors: a meta-analysis. Futur Oncol 2015; 11: 2471–84.

e77. Carlos G, Anforth R, Chou S, Clements A, Fernandez-Peñas P: A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab. Melanoma Res 2015; 25: 265–8.

e78. Naidoo J, Schindler K, Querfeld C, et al.: Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. Cancer Immunol Res 2016; 4: 383–9.

e79. Jour G, Glitza IC, Ellis RM, et al.: Autoimmune dermatologic toxicities from immune checkpoint blockade with anti-PD-1 antibody therapy: a report on bullous skin eruptions. J Cutan Pathol 2016; 43: 688–96.

e80. Anastasopoulou A, Papaxoinis G, Diamantopoulos P, et al.: Bullous pemphigoid-like skin lesions and overt eosinophilia in a patient with melanoma treated with nivolumab: case report and review of the literature. J Immunother 2018; 41: 164–7.

e81. Mochel MC, Ming ME, Imadojemu S, et al.: Cutaneous autoimmune effects in the setting of therapeutic immune checkpoint inhibition for metastatic melanoma. J Cutan Pathol 2016; 43: 787–91.

e82. Goldinger SM, Stieger P, Meier B, et al.: Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. Clin Cancer Res 2016; 22: 4023–9.

e83. Hwang SJE, Carlos G, Wakade D, et al.: Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. J Am Acad Dermatol 2016; 74: 455–61.

e84. Ohtsuka M, Miura T, Mori T, Ishikawa M, Yamamoto T: Occurrence of psoriasiform eruption during nivolumab therapy for primary oral mucosal melanoma. JAMA Dermatol 2015; 151: 797–9.

e85. Bonigen J, Raynaud-Donzel C, Hureaux J, et al.: Anti-PD1-induced psoriasis. A study of 21 patients. J Eur Acad Dermatol Venereol 2017; 31: e254–7.

e86. Schmutz JL: [Psoriasis and psoriatic arthritis induced by nivolumab (Opdivo®)]. Ann Dermatol Venereol 2016; 143: 881–2.

e87. Mutgi KAJ, Milhem M, Swick BL, Liu V: Pityriasis lichenoides chronica-like drug eruption developing during pembrolizumab treatment for metastatic melanoma. JAAD Case Rep 2016; 2: 343–5.

e88. Uemura M, Fa'ak F, Haymaker C, et al.: A case report of Grover's disease from immunotherapy - a skin toxicity induced by inhibition of CTLA-4 but not PD-1. J Immunother Cancer 2017; 5: 7.

e89. Burillo-Martinez S, Morales-Raya C, Prieto-Barrios M, Rodriguez-Peralto JL, Ortiz-Romero PL: Pembrolizumab-induced extensive panniculitis and nevus regression: two novel cutaneous manifestations of the post-immunotherapy granulomatous reactions spectrum. JAMA Dermatol 2017; 153: 721–2.

e90. Tetzlaff MT, Jazaeri AA, Torres-Cabala CA, et al.: Erythema nodosum-like panniculitis mimicking disease recurrence: a novel toxicity from immune checkpoint blockade therapy - report of 2 patients. J Cutan Pathol 2017; 44: 1080–6.

e91. Diem S, Keller F, Rüesch R, et al.: Pembrolizumab-triggered uveitis: an additional surrogate marker for responders in melanoma immunotherapy? J Immunother 2016; 39: 379–82.

e92. Nguyen AT, Elia M, Materin MA, Sznol M, Chow J: Cyclosporine for dry eye associated with nivolumab: a case progressing to corneal-perforation. Cornea 2016; 35: 399–401.

e93. Cappelli LC, Gutierrez AK, Baer AN, et al.: Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. Ann Rheum Dis 2017; 76: 43–50.

e94. Wilson MA, Guld K, Galetta S, et al.: Acute visual loss after ipilimumab treatment for metastatic melanoma. J Immunother Cancer 2016; 4: 66.

e95. Comito RR, Badu LA, Forcello N: Nivolumab-induced aplastic anemia: a case report and literature review. J Oncol Pharm Pract 2019; 25: 221–5.

e96. Palla AR, Kennedy D, Mosharraf H, Doll D: Autoimmune hemolytic anemia as a complication of nivolumab therapy. Case Rep Oncol 2016; 9: 691–7.

e97. Le Roy A, Kempf E, Ackermann F, et al.: Two cases of immune thrombocytopenia associated with pembrolizumab. Eur J Cancer 2016; 54: 172–4.

e98. Pföhler C, Eichler H, Burgard B, Krecké N, Müller CSL, Vogt T: A case of immune thrombocytopenia as a rare side effect of an immunotherapy with PD1-blocking agents for metastatic melanoma. Transfus Med Hemother 2017; 44: 426–8.

e99. Turgeman I, Wollner M, Hassoun G, Bonstein L, Bar-Sela G: Severe complicated neutropenia in two patients with metastatic non-small-cell lung cancer treated with nivolumab. Anticancer Drugs 2017; 28: 811–4.

e100. Tabchi S, Weng X, Blais N: Severe agranulocytosis in a patient with metastatic non-small-cell lung cancer treated with nivolumab. Lung Cancer 2016; 99: 123–6.

e101. Michot JM, Bigenwald C, Champiat S, et al.: Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016; 54: 139–48.

e102. Tardy MP, Gastaud L, Boscagli A, Peyrade F, Gallamini A, Thyss A: Autoimmune hemolytic anemia after nivolumab treatment in Hodgkin lymphoma responsive to immunosuppressive treatment. A case report. Hematol Oncol 2017; 35: 875–7.

e103. Del Castillo M, Romero FA, Argüello E, Kyi C, Postow MA, Redelman-Sidi G: The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis 2016; 63: 1490–3.

e104. Shiuan E, Beckermann KE, Ozgun A, et al.: Thrombocytopenia in patients with melanoma receiving immune checkpoint inhibitor therapy. J Immunother Cancer 2017; 5: 8.

e105. Menzies AM, Johnson DB, Ramanujam S, et al.: Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. J Clin Oncol 2017; 28: 368–76.

e106. Gutzmer R, Koop A, Meier F, et al.: Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. Eur J Cancer 2017; 75: 24–32.

e107. Johnson DB, Sullivan RJ, Ott PA, et al.: Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol 2016; 2: 234–40.

e108. Gettings EJ, Hackett CT, Scott TF: Severe relapse in a multiple sclerosis patient associated with ipilimumab treatment of melanoma. Mult Scler 2015; 21: 670.

e109. Kittai AS, Oldham H, Cetnar J, Taylor M: Immune checkpoint inhibitors in organ transplant patients. J Immunother 2017; 40: 277–81.

e110. Qin R, Salama AK: Report of ipilimumab in a heart transplant patient with metastatic melanoma on tacrolimus. Melanoma Manag 2015; 2: 311–4.

e111. Friend BD, Venick RS, McDiarmid SV, et al.: Fatal orthotopic liver transplant organ rejection induced by a checkpoint inhibitor in two patients with refractory, metastatic hepatocellular carcinoma. Pediatr Blood Cancer 2017; doi: 10.1002/pbc.26682.

e112. Tio M, Rai R, Ezeoke OM, et al.: Anti-PD-1/PD-L1 immunotherapy in patients with solid organ transplant, HIV, and hepatitis B/C infection. Eur J Cancer 2018; 104: 137–44.

e113. Munker S, de Toni EN: Use of checkpoint inhibitors in liver transplant recipients. United European Gastroenterol J 2018; 6: 970–3.

e114. Winkler JK, Gutzmer R, Bender C, et al.: Safe administration of an anti-PD-1 antibody to kidney-transplant patients: 2 clinical cases and review of the literature. J Immunother 2017; 40: 341–4.

e115. Herz S, Höfer T, Papapanagiotou M, et al.: Checkpoint inhibitors in chronic kidney failure and an organ transplant recipient. Eur J Cancer 2016; 67: 66–72.

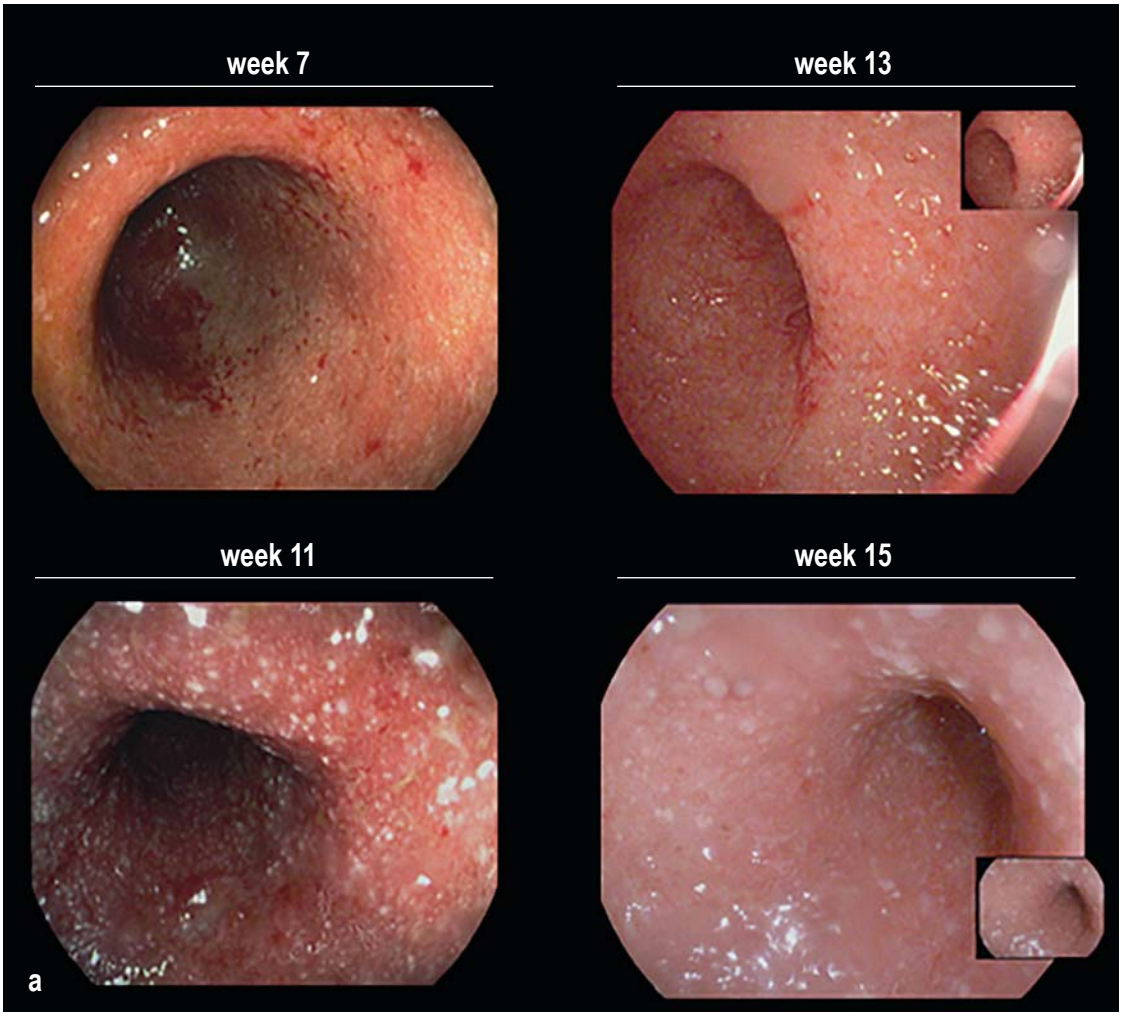
e116. Ong M, Ibrahim AM, Bourassa-Blanchette S, Canil C, Fairhead T, Knoll G: Antitumor activity of nivolumab on hemodialysis after renal allograft rejection. J Immunother Cancer 2016; 4: 64.

e117. El-Khoueiry AB, Sangro B, Yau T, et al.: Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017; 389: 2492–502.

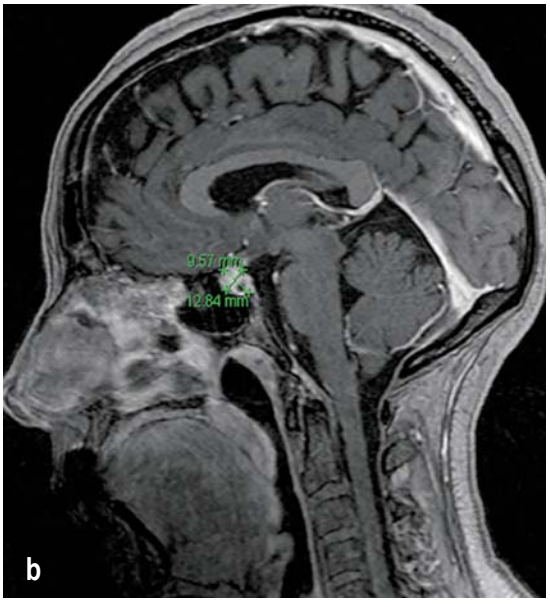
e118. Heppt MV, Schlaak M, Eigentler TK, et al.: Checkpoint blockade for metastatic melanoma and Merkel cell carcinoma in HIV-positive patients. Ann Oncol 2017; 28: 3104–6.

e119. Gay CL, Bosch RJ, Ritz J, et al.: Clinical trial of the anti-PD-L1 antibody BMS-936559 in HIV-1 infected participants on suppressive antiretroviral therapy. J Infect Dis 2017; 215: 1725–33.

e120. Knauss S, Ginesta Roque L, Hühnchen P, Heinzerling L, Böhmerle W, Endres M: [Neurological side effects of checkpoint inhibitors]. Nervenarzt 2018; doi: 10.1007/s00115–018–0571–8.



eFigure a) Colitis: Erythema and granular change of the rectosigmoid mucosa with contact vulnerability and contact hemorrhage. Endoscopic images (colon) in weeks 11 and 15 of treatment additionally show white punctate erosions and spots suggesting concomitant infection. (Reprinted from [34] with the kind permission of Taylor & Francis.)



eFigure b) An enlarged pituitary gland is seen in a woman with hypophysitis under treatment with ipilimumab. These MRI changes in the pituitary gland are not seen in all patients with hypophysitis.

eTABLE

Checkpoint inhibitors—their effects and the indications for which they are approved

Status	Drug	Target structure	Indications	Remarks	Antibody-dependent cytotoxicity (ADCC)	Half-life (circa)
Approved in the European Union	ipilimumab	CTLA-4	melanoma	human IgG1	yes	15 days
	nivolumab	PD-1	melanoma, non-small-cell lung cancer, renal-cell carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma	human IgG4	reduced	25 days
	pembrolizumab	PD-1	melanoma, non-small-cell lung cancer, classic Hodgkin's lymphoma, urothelial carcinoma	humanized IgG4	reduced	26 days
	avelumab	PD-L1	Merkel-cell carcinoma	human IgG1	yes	6 days
	atezolizumab	PD-L1	urothelial carcinoma, non-small-cell lung cancer	engineered human IgG1	no	27 days
Approved in the USA	durvalumab	PD-L1	lung cancer, bladder cancer, (head and neck tumors)	engineered human IgG1	no	18 days
	cemiplimab (REGN2810)	PD-1	squamous-cell carcinoma	human IgG4	reduced	19 days
Not (yet) approved	tremelimumab	CTLA-4	melanoma, pleural mesothelioma	human IgG2		
	urelumab, PF-2566	CD137/4-1BB	glioblastoma, lymphoma	humanized IgG4, human IgG2		
	relatlimab BMS-986016	LAG-3	melanoma, glioblastoma, pancreatic carcinoma, lymphoma	humanized IgG4		
	lirilumab	NK	leukemia, squamous-cell carcinoma	humanized IgG4		
	AMG228, TRX518, MK-4166	GITR	solid tumors	e.g., humanized IgG1		

CTLA-4: cytotoxic T-lymphocyte antigen-4; GITR: glucocorticoid-induced tumor necrosis factor-related protein; IgG: immunglobulin G; LAG-3: lymphocyte activation gene 3; NK: natural killer; PD-1: programmed death 1; PD-L1: programmed death-ligand 1